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***In vitro* Inhibition of Human Hepatic and cDNA-expressed Sulfotransferase Activity with
3-Hydroxybenzo[a]pyrene by Polychlorobiphenyls**

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Running Title: Hydroxy-PCBs inhibit sulfonation of 3-OH-BaP

Key words: polychlorobiphenyls; 3-hydroxy-benzo(a)pyrene; inhibition of sulfonation; SULT1A1*1 and SULT1A1*2; human liver cytosol; SULT1E1

Abbreviations: BaP, benzo[*a*]pyrene; BaP-3-SO₄, benzo[*a*]pyrene-3-sulfate; CB, chlorobiphenyl; CYP, cytochrome P450; OH-PCB, polychlorobiphenylol; 3-OH-BaP, 3-hydroxybenzo[*a*]pyrene; PAH, polycyclic aromatic hydrocarbon; PCB, polychlorinated biphenyl; PAPS, 3'-phosphoadenosine 5'-phosphosulfate; PCR, polymerase chain reaction; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; SULT, sulfotransferase; T4, thyroxine; TTR, transthyretin. Abbreviations for individual OH-PCBs are as recommended in Maervoet et al. 2004.

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Abstract

Sulfonation is a major phase II biotransformation reaction. We showed that several polychlorobiphenyls (OH-PCBs) inhibited the sulfonation of 3-hydroxybenzo(a)pyrene (3-OH-BaP) by human liver cytosol, and some cDNA-expressed sulfotransferases. At concentrations above 0.15 μM , 3-OH-BaP inhibited its own sulfonation in cytosol fractions that were genotyped for SULT1A1 variants, as well as with expressed SULT1A1*1, SULT1A1*2 and SULT1E1, but not with SULT1A3 or SULT1B1. The inhibition fit a two-substrate kinetic model. We examined the effects of OH-PCBs on the sulfonation of 0.1 or 1.0 μM 3-OH-BaP, respectively non-inhibitory and inhibitory substrate concentrations. At the lower 3-OH-BaP concentration, OH-PCBs with a 3-chloro-4-hydroxy-substitution pattern were more potent inhibitors of cytosolic sulfotransferase activity, with IC_{50} values between 0.33 and 1.1 μM , than OH-PCBs with a 3,5-dichloro-4-hydroxy-substitution pattern, which had IC_{50} values from 1.3 to 6.7 μM . We found similar results with expressed SULT1A1*1 and SULT1A1*2. The OH-PCBs were considerably less potent inhibitors when assay tubes contained 1.0 μM 3-OH-BaP. The inhibition mechanism was non-competitive, and our results suggested the OH-PCBs competed with 3-OH-BaP at an inhibitory site on the enzyme. The OH-PCBs tested inhibited sulfonation of 3-OH-BaP by SULT1E1, but the order of inhibitory potency was different than for SULT1A1. SULT1E1 inhibitory potency correlated with the dihedral angle of the OH-PCBs. The OH-PCBs tested were generally poor inhibitors of SULT1A3 and SULT1B1-dependent activity with 3-OH-BaP. These findings demonstrate an interaction between potentially toxic hydroxylated metabolites of PCBs and polycyclic aromatic hydrocarbons, which could result in reduced clearance by sulfonation.